Efficient derivation of cortical glutamatergic neurons from human pluripotent stem cells: a model system to study neurotoxicity in Alzheimer's disease.

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Public Summary:
Alzheimer's disease (AD) is among the most prevalent forms of dementia affecting the aging population, and pharmacological therapies to date have not been successful in preventing disease progression. Therapeutic efforts may benefit from the development of models that enable basic investigation of early disease pathology, and assessment of the impact of neurotoxic agents in AD on specific neuronal populations. Since AD is generally known to be toxic to glutamatergic circuits, we differentiated glutamatergic neurons from human embryonic stem cells, and exposed them to beta amyloid oligomers ("globulomers") correlated with the level of cognitive deficits in AD. Globulomer-treated glutamatergic neurons yielded signs of the disease, including cell culture age-dependent binding of Abeta and cell death. Abeta-induced toxicity was selective for glutamatergic rather than GABAeric neurons present in our cultures, consistent with previous findings in postmortem human AD brain. This disease-relevant model offers a system to generate human neuronal cell types specifically affected by AD, for study of AD pathology and assessment of potential therapies.

Scientific Abstract:
Alzheimer's disease (AD) is among the most prevalent forms of dementia affecting the aging population, and pharmacological therapies to date have not been successful in preventing disease progression. Future therapeutic efforts may benefit from the development of models that enable basic investigation of early disease pathology. In particular, disease-relevant models based on human pluripotent stem cells (hPSCs) may be promising approaches to assess the impact of neurotoxic agents in AD on specific neuronal populations and thereby facilitate the development of novel interventions to avert early disease mechanisms. We implemented an efficient paradigm to convert hPSCs into enriched populations of cortical glutamatergic neurons emerging from dorsal forebrain neural progenitors, aided by modulating Sonic hedgehog (Shh) signaling. Since AD is generally known to be toxic to glutamatergic circuits, we exposed glutamatergic neurons derived from hESCs to an oligomeric pre-fibrillar forms of Abeta known as "globulomers", which have shown strong correlation with the level of cognitive deficits in AD. Administration of such Abeta oligomers yielded signs of the disease, including cell culture age-dependent binding of Abeta and cell death in the glutamatergic populations. Furthermore, consistent with previous findings in postmortem human AD brain, Abeta-induced toxicity was selective for glutamatergic rather than GABAeric neurons present in our cultures. This in vitro model of cortical glutamatergic neurons thus offers a system for future mechanistic investigation and therapeutic development for AD pathology using human cell types specifically affected by this disease.